# Synthesis of (−)-7-Epiaustraline and (−)-1-Epicastanospermine

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*Received December 23, 1999*

Highly efficient and selective syntheses of the title compounds are described. The cornerstone of the synthetic plan is the tandem inter [4 + 2]/inter [3 + 2] cycloaddition process. These syntheses differ from previous applications of this strategy in that they incorporate an alkylation in the hydrogenolysis step to close the second ring of the azabicyclic systems. Notable features of the sequence are (1) the highly regio- and stereoselective [3 + 2] cycloaddition of nitronate **15** with siloxymethyl (*Z*)-*β*-silylvinyl ketone (*Z*)-**22b** and (2) the highly selective reduction of the resulting ketone **24a** with L-Selectride. A single-crystal X-ray structure analysis of synthetic (−)-7-epiaustraline confirmed that the targeted structure was successfully synthesized. This stimulated a reexamination of the structural assignment of the natural product. (−)-1-Epicastanospermine was synthesized in four steps from the common intermediate **27a**. The absolute configuration of (−)-1-epicastanospermine was assured by single-crystal X-ray structure analysis of intermediate (−)-**27a.** Thus, the sign of the optical rotation had to be revised. The overall efficiency of these syntheses were 9 steps and 23% yield for (−)-7-epiaustraline and 10 steps and 20% yield for (−)-1-epicastanospermine

## Introduction

**Alexines and Australines.** In 1988, a colorless, cubic solid was isolated from the aqueous ethanolic extracts of finely ground, dried, pod of *Alexa leiopetala* Sandwith.[1] Single-crystal X-ray analysis revealed that the isolated compound, (+)-alexine ((+)-**1**), was a pyrrolizidine bearing a hydroxymethyl group adjacent to the ring nitrogen [C(3)], Figure 1. The isolation of alexine was a significant departure from the broad class of pyrrolizidine alkaloids which bear carbon substituents at C(1).[2] Furthermore, the structural similarity to DMDP (**11**) suggested that alexine may also possess glycosidase inhibitory activity. Inhibition studies using *β*-glucosidase and *β*-galactosidase enzymes from mouse small intestines and *β*-glucosidase from *Penicillium expansum* revealed that alexine was indeed a glucosidase inhibitor, although weaker than DMDP.[3] Alexine was also shown to inhibit thioglucosidase enzymes isolated from *Brevicoryne brassiae*.[11]

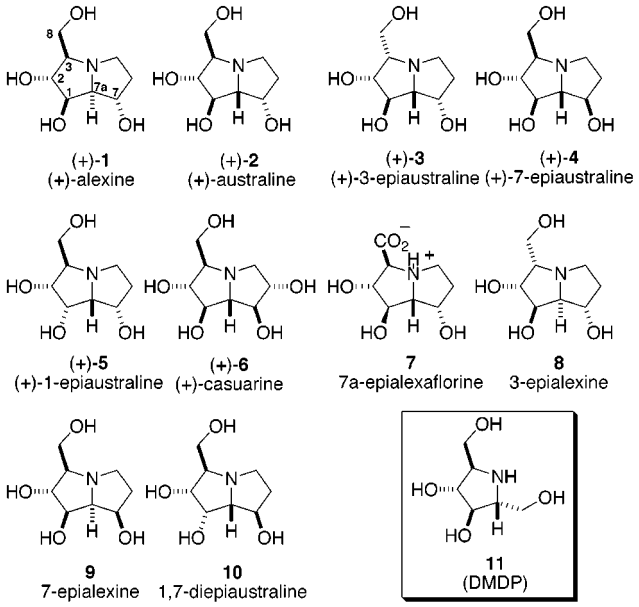



**Figure 1.** (+)-Alexine, (+)-australine, and related alkaloids.

Shortly after the isolation of alexine, a second isomer was isolated from the seeds of *Castanospermum australe*.[4] (+)-Australine ((+)-**2**) was found to be a C(7a) epimer of alexine by X-ray crystallographic analysis. Enzyme inhibition studies indicated that the alkaloid was a potent inhibitor of amyloglucosidase[4] and the glycoprotein-processing enzyme glucosidase I but a weak inhibitor of glucosidase II.[5] No inhibition of *β*-glucosidase,

(1) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487.

(2) (a) Wrobel, J. T. Pyrrolizidine Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Chapter 7. (b) Robins, D. J. Pyrrolizidine Alkaloids. *Prog. Chem. Org. Nat. Prod.* **1982**, *41*, 115. (c) Dai, W.-M.; Nagao, Y.; Fujita, E. *Heterocycles* **1990**, *30*, 1231. (d) Robins, D. J. *Nat. Prod. Rep.* **1993**, 487 and references to earlier reviews. (e) Neuberger, A.; Tatum E. L. *Frontiers of Biology: The Pyrrolizidine Alkaloids*; North-Holland Publishing Company: Amsterdam, 1968; Vol. 9. (f) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proc. Int.* **1996**, 643. (g) For a review of the reported syntheses of hydroxylated pyrrolizidine alkaloids see: Giovanni, C.; Zanardi, F.; Rassu, G.; Pinna, L. in *Advances in the Stereoselective Synthesis of Hydroxylated Pyrrolizidines*.

(3) Scofield, A. M.; Rossiter, J. T.; Witham, P.; Kite, G. C.; Nash, R. J.; Fellows, L. E. *Phytochemistry* **1990**, *29*, 107.

(4) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198.

(5) Tropea, J. E.; Molyneux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027.

(6) Nash, R. J.; Fellows, L. E.; Plant, A. C.; Fleet, G. W. J.; Derome, A. E.; Baird, P. D.; Hegarty, M. P.; Scofield, A. M. *Tetrahedron* **1988**, *44*, 5959.

(7) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111.

(8) Harris, C. M.; Harris, T. M.; Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *Tetrahedron Lett.* **1989**, *30*, 5685.

(9) Nash, R. J.; Thomas, P. I.; Waigh, R. D.; Fleet, G. W. J.; Wormald, M. R.; Lilley, P. M.de Q.; Watkin, D. J. *Tetrahedron Lett.* **1994**, *35*, 7849.

(10) Pereira, A. C. de S.; Kaplan, M. A. C.; Maia, J. G. S.; Gottlieb, O. R.; Nash, R. J.; Fleet, G. W. J.; Watkin, D. J.; Scofield, A. M. *Tetrahedron Lett.* **1991**, *47*, 5637.

(11) Fleet, G. W. J.; Haraldsson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 5441.

10.1021/jo991990d CCC: $19.00 
Published on Web 03/23/2000

α- or β-mannosidase, and α- or β-galactosidase was observed.[5] In the next few years, several additional isomers of alexine and australine were isolated. Among them were (+)-3-epiaustraline ((+)-**3**),[6] (+)-7-epiaustraline ((+)-**4**),[7] (+)-1-epiaustraline ((+)-**5**),[7,8] (+)-casuarine ((+)-**6**),[9] and the related amino acid 7a-epialexaflorine (**7**).[10] During the course of studies on the synthesis of several of those natural products, additional epimers were created as a consequence of the synthetic routes chosen. Among them, synthetic 3-epialexine (**8**),[11] 7-epialexine (**9**),[12] and 1,7-diepiaustraline (**10**)[13] were produced. The most profound property that all of the members of this class of alkaloids possess is glucosidase inhibition to varying degrees. For example, a comparative study of inhibition of the glucan 1,4 α-glucosidase hydrolysis of potato amylose among the naturally occurring pyrrolizidine alkaloids **1**−**5** indicated that each isomer was a potent inhibitor.[7] Relative to castanospermine ($IC_{50} = 1.5 \times 10^{-6}$ M), a potent glucosidase inhibitor, (+)-alexine ((+)-**1**) was found to be the weakest ($IC_{50} = 1.1 \times 10^{-5}$ M) and 7-epiaustraline (**4**) the strongest ($IC_{50} = 1.3 \times 10^{-7}$ M).

To date, seven of the alexine epimers have been prepared synthetically by a variety of approaches. 7-Epialexine (**9**) and (+)-7-epiaustraline ((+)-**4**) have been prepared from L-xylose by the reductive cyclization of azido epoxides.[12] The formation of alkaloid (+)-**4** was surprising since (+)-australine ((+)-**2**) was the initial target. Since comparison of spectra for synthetic **2** matched only that reported for isolated (+)-**4**, the authors were forced to conclude that an unusual inversion at C(7) had occurred in the epoxide opening. (+)-1-Epiaustraline ((+)-**5**) and 1,7-diepiaustraline (**10**) were synthesized from heptonolactones by the reductive cyclization of azido epoxides.[13] Australines (+)-**5** and **10** were also synthesized from pyroglutamic acid.[14] Alexine ((+)-**1**), 3-epialexine (**8**), and 7-epialexine (**9**) were synthesized from D-glucose through the intermediacy of methyl 2-azido-3-*O*-benzyl-2-deoxy-α-mannofuranoside.[11] Throughout those approaches, two main synthetic strategies are common; the formation of pyrrolidine rings by reductive cyclizations of azido epoxides and annulation by *N*-alkylation. Common to all syntheses was the use of sugars or sugar-derived building blocks as starting materials.

**Castanospermine and Related Diastereoisomers.** Castanospermine was first isolated as a cubic, crystalline solid from the aqueous ethanolic extracts of finely ground immature seeds of *Castanospermum australe*.[15] Extensive 2-D NMR analysis revealed that the isolated compound was a tetrahydroxyindolizidine. The finding was confirmed by an X-ray crystal analysis which also established the relative configuration of all five stereogenic centers in (+)-castanospermine ((+)-**12**). The structural elucidation of castanospermine also revealed that the alkaloid bore a strong resemblance to both (+)-australine ((+)-**2**) and D-glucose. Not surprisingly, the absolute configuration was determined by a synthesis of the alkaloid from D-glucose to be as depicted in Figure 2.[16] Since then, numerous syntheses of natural, unnatural, and racemic castanospermine have been completed.[17]

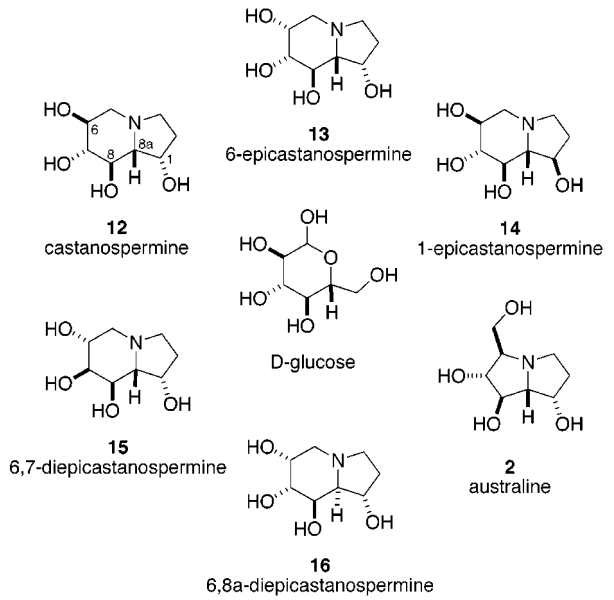



**Figure 2.** Castanospermine and related diastereoisomers.

Castanospermine displays an impressive breadth of biological activity including α- and β-glucosidase inhibition and carcinoma, viral, and retroviral suppression.[18] Those properties, combined with the functional density of castanospermine prompted the search for additional natural and unnatural analogues.[17b] Among those, (+)-1-epicastanospermine ((+)-**14**),[19] a synthetic diastereomer, provided the impetus to explore the application of the tandem cycloaddition chemistry of nitroalkenes.

**Tandem [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes.** Over the past nine years we have described the development and application of the tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes as a powerful strategy for heterocycle synthesis.[20] The tandem cycloaddition process has been successfully applied to the synthesis of a variety of alkaloids including platynecine,[20b] rosmarinecine,[20c] crotanecine,[20d] mesembrine,[20e] detoxinin[20f] castanospermine,[17a] 6-epicastanospermine,[17a] australine,[17a] and 3-epiaustraline.[17a] All of these compounds have been synthesized by use of the intermolecular [4 + 2] cycloaddition followed by intramolecular [3 + 2] cycloaddition strategy. In addition, the double-intermolecular tandem sequence has been successfully used in the synthesis of hastanecine,[20g] macronecine,[20h] and casuarine.[20i,j]

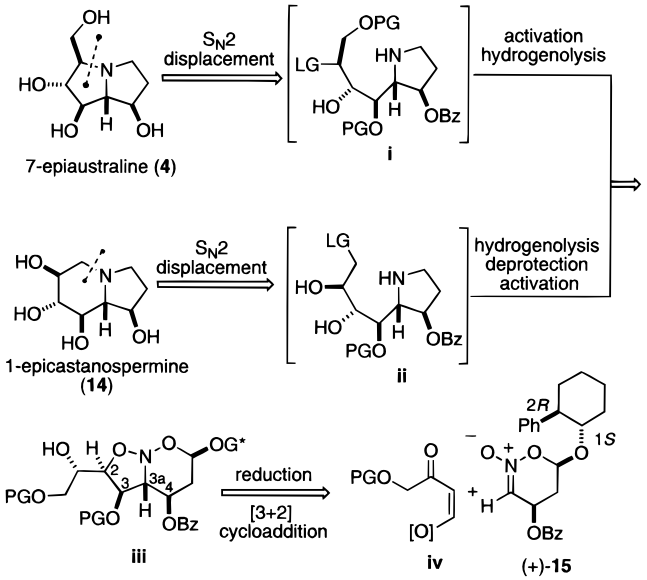
We undertook the synthesis of (+)-7-epiaustraline ((+)-**4**) as our entree into the alexine/australine class of pyrrolizidines. The placement of the hydroxymethyl

(12) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513.
(13) Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517.
(14) Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553.
(15) Hohenshutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.
(16) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165.
(17) (a) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046 and references cited. Reviews on castanospermine and diastereomers: (b) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. (c) Michael, J. P. *Nat. Prod. Rep.* **1997**, 21.
(18) Winchester, B. G.; Cenci di Bello, I.; Richardson, A. C.; Nash, R. J.; Fellows, L. E.; Ramsden, N. G.; Fleet, G. W. J. *Biochem. J.* **1990**, *269*, 227.
(19) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52 and referenced cited therein.
(20) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Denmark, S. E.; Parker, D. L.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 435. (c) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266. (d) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (f) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (g) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672. (h) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045. (i) Denmark, S. E.; Hurd, A. R. *Org. Lett.* **1999**, *1*, 1311. (j) Denmark, S. E.; Hurd, A. R. *J. Org. Chem. 2000*, *65*, 2875.

group at C(3) and the additional oxygen substituent at C(1) mandated an alternative strategy to our previously employed syntheses of necine bases. Once the strategy was formulated (see below) it was apparent that the indolizidine skeleton was also readily accessed by simple functional group manipulations, thus allowing the synthesis of 1-epicastanospermine from the same intermediate. We detail below the successful realization of this strategy which indeed culminated in the synthesis of (+)-7-epiaustraline[21] and 1-epicastanospermine. However, it has been found that (+)-7-epiaustraline is not a natural product and thus has stimulated a reevaluation of the assignment of various pyrrolizidine structures.[22]

**Synthetic Strategy: Selective Activation−Alkylation.** The strategy for the synthesis of both targets is depicted in Scheme 1. We envisioned the formation of bicyclic amines (+)-**4** and (+)-**14** by the alkylation of the pyrrolidine liberated from the hydrogenolysis of a suitably functionalized nitroso acetal (**iii**). This flexibility in this strategy is apparent. The hydroxymethyl group of 7-epiaustraline could be introduced by C−N bond formation in an $S_N2$ displacement reaction at an activated secondary carbinol such as **i**. The indolizidine skeleton could be created by an $S_N2$ displacement at the activated primary carbinol center in **ii**. The success of the strategy thus hinged on the ability to differentiate between and activate either the primary or secondary alcohol at will. The formation of the secondary alcohol was planned as a selective reduction of the carbonyl group needed to activate the dipolarophile **iv** in the [3 + 2] cycloaddition. The 1,2-cis relationship of the hydrogen atoms at C(2) and C(3) in **iii** augured for the use of a *Z*-configured dipolarophile. The trans relationship between C(3) and C(3a) mandates an exo selective [3 + 2] cycloaddition from the face of the nitronate opposite the C(4) substituent. Furthermore, the 1,2-trans relationship between the hydrogen atoms at C(3a) and C(4) of the nitroso acetal would arise from an intermolecular [3 + 2] cycloaddition between the dipolarophile bearing an oxygen function at the terminus and a nitronate bearing an oxygen function at C(4). Taken in together, the nitroso acetal **iii** would be created by the cycloaddition between vinyl ketone **iv** and nitronate (+)-**15**.[20g]

**Scheme 1**

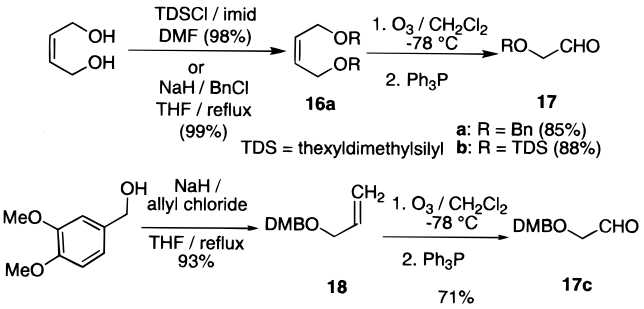



Several issues embodied in this strategy required further consideration. Foremost was the influence of an oxygen substituent at the $\beta$-terminus of the dipolarophile on the regiochemical outcome of the [3 + 2] cycloaddition. From previous studies on the effects of substituent on the [3 + 2] cycloaddition, we knew that the dipolarophile had to contain a silicon moiety as a surrogate for oxygen to obtain the correct regiochemical result in the [3 + 2] cycloaddition.[23] Our second concern was the facial diastereoselectivity in the [3 + 2] cycloaddition. On the basis of the foregoing studies, we anticipated this process to occur selectively in an exo fashion in an approach to the dipole from the face opposite the C(4) benzoate.[23] Less certain, however, was the ability to stereoselectively reduce the carbonyl group in the nitroso acetal and selectively activate either the primary or secondary alcohols.

## Results and Discussion

**Dipolarophile Synthesis.** Consideration of the design elements outlined above led to the formulation of $\beta$-silylvinyl ketone (*Z*)-**22** (Scheme 3) as the ideal dipolarophile for the [3 + 2] cycloaddition. However, because selection of the specific protecting group could only be dictated by reactions after cycloaddition, three choices were carried forward simultaneously. Synthesis of **22** began with the preparation of protected α-alkoxyacetaldehydes **17** in two steps from 2-butene-1,4-diol or allyl chloride by straightforward diprotection and ozonolysis (Scheme 2).

**Scheme 2**




Installation of the *cis*-alkene for the dipolarophile was accomplished as outlined in Scheme 3. Addition of the bromomagnesium derivative of silyl acetylene **19**[24] to aldehyde **17a** provided the propargyl alcohol **20a** in 85% yield. Semi-hydrogenation of the alkynes **20a**−**c**[25] with a myriad of catalysts was plagued by irreproducibility and over-reduction.[26] Alternative protocols aimed at increasing the reduction selectivity were also examined without success, including polymer-bound nickel boride[27] (variable selectivities), DIBAL-H in THF at reflux[28] (only 31% conversion), DIBAL−H·$Et_3N$[29] (8/1 *Z*/*E* but incomplete reaction), and diisoamylborane in THF[30] (failed to provide the alkene). However, reaction of **20b** with 2

(21) A preliminary disclosure has already appeared. Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357.

(22) Wormald, M. R.; Nash R. J.; Hrnicar, J. D.; White, J. D.; Molyneaux, R. J.; Fleet, G. W. *Tetrahedron: Asymmetry* **1998**, *9*, 2549.

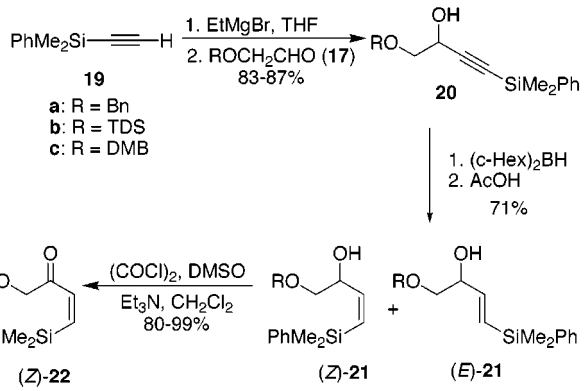
(23) Denmark, S. E.; Seierstad, M. J.; Herbert, B. *J. Org. Chem.* **1999**, *64*, 4, 884.

(24) Fleming, I.; Takai, K.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269.

(25) Reviews: (a) Seigel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, ch. 3.1, p 417. (b) Marshall, E. N.; Li, T. *Synthesis* **1973**, 457.

equiv of dicyclohexylborane,[30] followed by addition of acetic acid resulted in a clean conversion to the *cis*-alkene with no other olefinic material detectable. Upon purification by chromatography and distillation, (*Z*)-**21b** was secured in 71% yield.

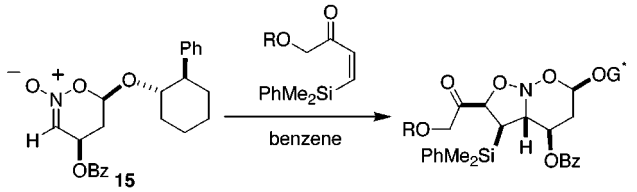
**Scheme 3**




The Swern oxidation of alcohols **21a**−**c** proceeded uneventfully to provide the (*Z*)-*β*-silylvinyl ketones **22a**−**c** in 80−99% yield. In all cases the vinyl ketones could be purified by chromatography on both alumina (neutral III) and silica gel without isomerization. Final purification by distillation of the liquid ketones was not possible. Extensive isomerization to the trans alkene was noted even at $10^{-5}$ mmHg vacuum.

**[3 + 2] Cycloaddition.** The thermal cycloaddition reaction between nitronate **15** and dipolarophiles **22a**−**c** was a facile process. The diastereomeric ratio was considerably higher than for monosubstituted dipolarophiles,[23] as were the isolated yields, Table 1. For example, the reaction between **15** and (*Z*)-**22a** provided the corresponding nitroso acetal (**23**) in 98% yield as a 32/1 ratio of diastereomers. The reaction was essentially complete after 4 h at room temperature. Comparison of the $^1$H and $^{13}$C NMR chemical shifts of HC(2), HC(3), and HC(3a) supported the assignment that the major nitroso acetal was formed as a head-to-head regioisomer, Table 2. In the minor isomer, the $^1$H NMR resonance of HC(2) was shifted upfield by 0.36 ppm relative to the major isomer. While not entirely convincing, that difference was clearly within the range noted in the cycloaddition studies on simple, monosubstituted dipolarophiles where the major and minor isomers were determined to be endo-exo isomers.[23] Comparison of the $^{13}$C chemical shifts were not consistent with the identity of nitroso acetals **23a** and **23b** as endo-exo isomers.[23] The resonance for C(2) in the

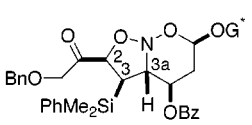
**Table 1. [3 + 2] Cycloadditions of 15 with Dipolarophiles 22**

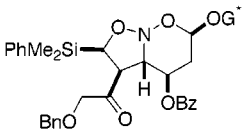



| dipolarophile | R | product | dr[a] | yield, % |
|---|---|---|---|---|
| **22a** | Bn | **23** | 32/1 | 98 |
| **22b** | TDS | **24** | 26/1 | 97 |
| **22c** | DMB | **25** | 32/1 | 100 |

[a] Ratios determined by $^1$H NMR (500 MHz) analysis.

**Table 2. Selected NMR Data for Major and Minor Nitroso Acetals 23**




**23a (major)** **23b (minor)**

| major | | | minor | | |
|---|---|---|---|---|---|
| carbon | $^1$H (ppm) | $^{13}$C (ppm) | carbon | $^1$H (ppm) | $^{13}$C (ppm) |
| C(2) | 5.06 | 88.6 | C(2) | 4.70 | 78.8 |
| C(3) | 2.31 | 32.1 | C(3) | 3.81 | 52.8 |
| C(3a) | 3.71 | 74.6 | C(3a) | 3.87 | 78.6 |

minor isomer was located 9.8 ppm upfield from the major isomer. Furthermore, comparison of the $^1$H and $^{13}$C NMR chemical shifts at C(3) was instrumental in deciphering the identity of the isomers. The $^1$H NMR resonance of C(3) in the major isomer was found at *1.5 ppm upfield* from that of the minor, suggesting that the silicon atom was directly attached there. The carbon resonances also supported that assignment. The resonance for C(3) of the major nitroso acetal was located at 32.1 ppm while the resonance for C(3) of the minor isomer was located at 52.8 ppm. The positional differences clearly indicate that an electron-withdrawing group was attached at C(3) of the minor isomer. Comparison with data for similar *Z*-*β*-silyl-substituted dipolarophile cycloadditions[23] was also consistent with the identity of the minor isomer as a regioisomer.

In accord with our [3 + 2] cycloaddition studies with nitronate **15**, both isomers were assigned structures consistent with the approach of the dipolarophile from the face opposite the C(4) benzoate.[20g] The issues surrounding stereoselectivity (endo-exo and diastereofacial) have been discussed previously.[23] It is sufficient to state that once again an extremely high tendency toward approach of the dipolarophile to the face of the nitronate opposite the C(4) substituent is a combined result of the kinetic anomeric effect and the conformation of the nitronate.

**Ketone Reduction Studies.** Creation of the secondary carbinol stereocenter of appropriate configuration was planned as a selective reduction of the carbonyl group under the influence of the adjacent stereocenter of the nitroso acetal. Whereas models for the sense of stereoinduction could be constructed, their predictive value with regard to the actual course of reduction was such that a sampling of reagents thought to respond to both Felkin-type control[31] and a chelation control[32] were tested. From the results of a survey of reagents in the

(26) For example, hydrogenation of alkyne **20a** over 5% palladium on calcium carbonate in the presence of quinoline (6 mol %) provided a 5/1 mixture of *Z*- (42%) and *E*- (7)% allylic alcohols ((*Z*)-**21a** and (*E*)-**21a**) in addition to the saturated product (18%). The use of 1 mol equiv of quinoline (relative to substrate) failed to suppress over-reduction. The use of 5% palladium on calcium carbonate poisoned with lead (Lindlar catalyst) offered no advantages. The reduction times were significantly extended (11 h vs 3 h) and resulted in lower (2−4/1) *Z*/*E* selectivities. Hydrogenation over palladium on barium sulfate also resulted in low and variable selectivity.

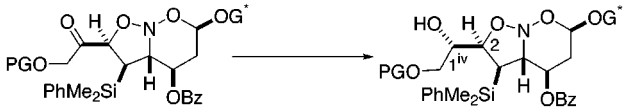
(27) (a) Choi, J.; Yoon, N. M. *Tetrahedron Lett.* **1996**, *37*, 1057. (b) Yoon, N. M.; Park, K. B.; Lee, H. J.; Choi, J. *Tetrahedron Lett.* **1996**, *37*, 8527.

(28) Review: Pasto, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, Ch 3.3, p 471.

(29) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520.

(30) Brown, H. C. *Organic Synthesis via Boranes*; John Wiley & Sons: New York, 1975; pp 29 and 100.

**Table 3. L-Selectride Reduction Selectivities**



| ketone | alcohol | dr[a] | yield, % |
|---|---|---|---|
| (**23a**) Bn | **26** | >20//1 | 83 |
| (**24a**) TDS | **27** | 14/1 | 87 |
| (**25a**) DMB | **28** | >20/1 | 99 |

[a] Ratios determined by $^1$H NMR (500 MHz) analysis.

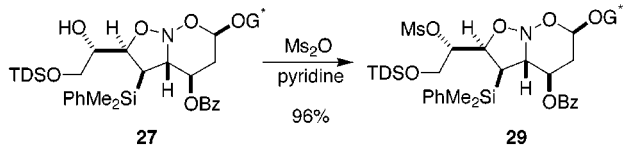
reduction of simpler model ketones[33] it was clear that maximal selectivity was obtained when L-Selectride was used as the hydride source and the α-alkoxymethyl ketone was protected as a benzyl ether. Not surprisingly, reduction of the ketone **23a** with L-Selectride at −74 °C provided the pair of epimeric alcohols **26** in excellent diastereoselectivity (>20/1, 83%), Table 3.

Examination of the $^1$H NMR coupling constants of the newly created stereogenic center [C(1$^{iv}$)] and at C(2) of the nitroso acetal revealed that those protons did not couple. The inference was that the protons were aligned at a 90° angle and that no information regarding the sense of stereoselection could be obtained. As expected, similar reduction selectivity was observed for DMB-protected ketone **25a** with L-Selectride. However, we were gratified to discover that silyl protected ketone **24a** also underwent reduction with L-Selectride with high stereoselectivity. The diastereomeric alcohols **27** were obtained in a 14/1 ratio. The protons at the newly created stereogenic center [C(1$^{iv}$)] and at C(2) of the nitroso acetal did not couple, suggesting that the sense of stereochemical induction was the same as with ketones **23** and **25**. Fortunately, both major reduction products **26a** and **27a** were obtained as solids. Crystals of each carbinol suitable for X-ray analysis were obtained by slow crystallization. The analysis of carbinol **26a** confirmed that the reduction had proceeded to afford the *S*-configuration at the newly created center. Thus, the relative configuration of all five stereogenic centers required for the proposed syntheses of (+)-7-epiaustraline and (−)-1-epicastanospermine were correct. Much to our delight, the X-ray crystal structure analysis of carbinol **27a** confirmed our suspicion that the Selectride reduction of ketone **24a** occurred in the same stereochemical sense as in ketones **23** and **25** (see Supporting Information). Since carbinol **27a** was prepared from nitronate (+)-**15** containing the (1*S*,2*R*)-phenylcyclohexyloxy substituent, the relative and absolute configurations were secured.

The same sense of stereochemical induction for benzyl- and thexyldimethylsilyl-protected α-alkoxymethyl ketones is inconsistent with the delivery of the hydride from a species coordinated to the ether oxygen. Consequently, an alternative control element must be operative. The remarkable selectivity and sense of induction can be rationalized with the aid of ground-state energy minimization calculations[34] of ketone **24** which provided two low energy conformers, Figure 3. In conformer **vii**, the carbonyl is oriented away from the nitroso acetal ring system in such a way as to minimize through-space interactions with the phenyl ring attached to the silicon atom and to minimize dipole interactions with the adjacent nitroso acetal C−O bond. In conformer **viii**, the carbonyl is oriented in the opposite direction, toward the nitroso acetal ring. While the relative energy of these conformers in the ground state without the reagent is not necessarily relevant, it is noteworthy that in both of these conformers the phenyl ring of the phenyldimethylsilyl group is shielding one face of the carbonyl preferentially. The conformer (**vii**) that leads to the major reduction product corresponds to the Cornforth[35] model for carbonyl reductions.

**Activation of the Secondary Alcohol.** With all five contiguous stereogenic centers required for the synthesis of both targets installed with high selectivity we could now turn our attention to the activation of the secondary carbinol for the critical ring closure. The transformation of the alcohol to a mesylate or a tosylate proved more challenging than expected. Reaction of alcohols **26** and **27** with equimolar quantities of methanesulfonyl chloride or 4-toluenesulfonyl chloride in the presence of a variety of bases (triethylamine, Hünig base, pyridine, 2,6-lutidine, sodium hydride, methyllithium) in methylene chloride or THF failed to provide the corresponding sulfonate esters. To our delight, methanesulfonic anhydride[36] (6 equiv) was found to react cleanly with alcohol **27** in *5 min* when pyridine was used as the solvent (Scheme 4). Although stable indefinitely in vacuo, mesylate **29** decomposed gradually upon exposure to air and rapidly in solution.

**Scheme 4**



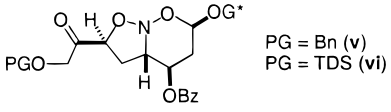
Unfortunately benzyl protected carbinol **26** resisted activation under these conditions as well. We then resorted to trapping the reduction product from **23** and **25** in situ with various triflating and sulfonylating agents, none of which proved successful.[37,38] At this stage the use of the benzyl ether type protecting groups was abandoned.

These difficulties prompted us to consider liberating the primary alcohol in order to deliver the activating group to the secondary alcohol in an intramolecular process. The intermediate diol would also allow access to the doubly activated substrates such as cyclic sulfate or epoxide which would make intriguing precursors for closure.

(31) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

(32) Hoveyda, A. H.; Evans. D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(33) Reduction of model ketones **v** and **vi** with a variety of reducing agents provided initial leads. For **v** L-Selectride gave 19/1 selectivity but no reagent was found to give good selectivities with **vi**.



(34) Molecular Mechanics calculations executed with the Spartan calculation package on a CAChe machine.

(35) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, *112*.

(36) Field, L.; Settlage, P. H. *J. Am. Chem. Soc.* **1954**, *76*, 1222.

(37) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1996**, *74*, 77, and references therein.

(38) Introduction of the mesylate by [3 + 2] cycloaddition with the dipolarophile bearing the activating group (allylic mesylate) was also unsuccessful. The nitronate decomposed prior to reacting with the dipolarophile at both ambient temperature and at 80 °C.

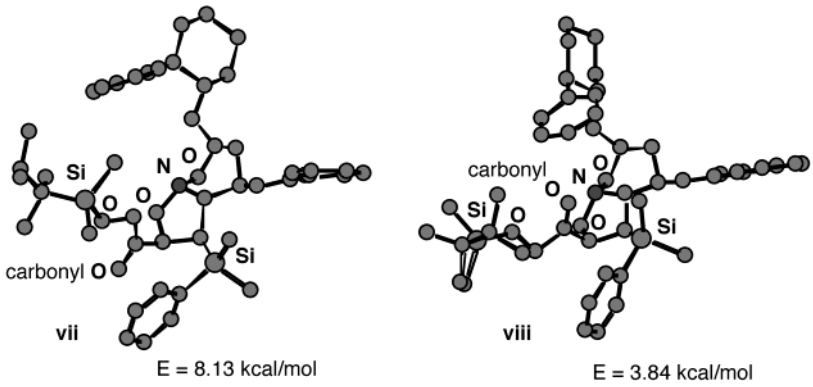
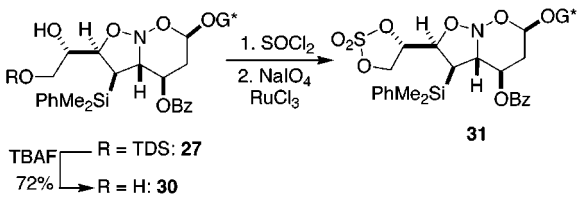



**Figure 3.** Ketone **24a** conformations calculated using molecular mechanics.

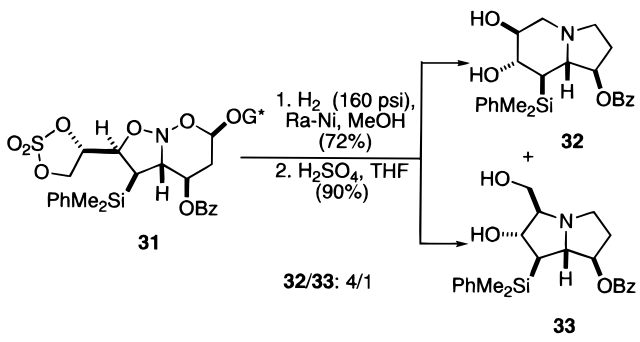
The reaction of silyl ether **27** with 1.3 equiv of TBAF resulted in the rapid removal of the silyl protecting group to afford the diol **30** in 72% yield, Scheme 5. The diol was allowed to react with an excess of thionyl diimidazole[39] in THF to furnish the cyclic sulfite in 85% yield as a 1.2/1 mixture of sulfur epimers. Oxidation of the sulfite to the sulfate occurred smoothly and quantitatively using ruthenium (III) chloride and sodium periodate.[40] Sulfate **31** was subsequently found to be somewhat unstable, surviving rapid chromatography with a polar solvent but not recrystallization.

**Scheme 5**



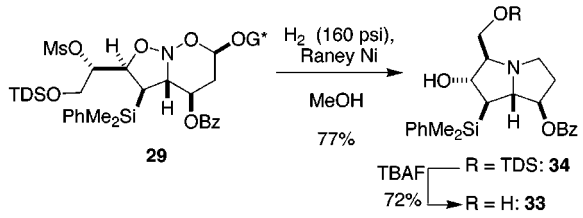

**Hydrogenolysis Studies.** With a number of activated substrates in hand, we could evaluate the crucial hydrogenolysis/ring closure construction of the azabicyclic nucleus. We began with the cyclic sulfate **31** to ascertain the relative preference for closure to a pyrrolizidine versus an indolizidine. Hydrogenation of **31** with Raney nickel in methanol at 160 psi for 36 h provided a 4/1 mixture of sulfate salts in 72% yield, Scheme 6. Liberation of the free base was accomplished in 90% yield by the addition of 1 equiv of concentrated $H_2SO_4$ to a THF suspension of the salt mixture.[41] NMR (COSY) analysis indicated that the major product possessed the indolizidine skeleton (**32**) and that the minor product was the pyrrolizidine isomer (**33**).

**Scheme 6**




With authentic samples of both azabicyclic compounds in hand, we next studied the hydrogenation of mesylate **29**. At 160 psi of hydrogen in the presence of Raney nickel, **29** furnished pyrrolizidine **34** in 77% yield with 98% recovery of the auxiliary, Scheme 7. This reduction was insensitive to hydrogen pressure as evidenced by comparable yields at 160, 260, and 360 psi (72−74%). Removal of the silyl ether protecting group afforded the familiar primary alcohol **33** in 72% yield which was identical to material obtained from the hydrogenolysis of the cyclic sulfate.

**Scheme 7**



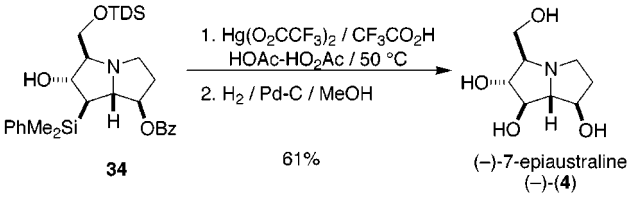

The isolation of pyrrolizidine **34** in high yield from simple hydrogenolysis validated our expectation that the hydrogenolytic cascade could be terminated successfully by an alkylation in addition to the many acylations that had been described. The lack of isolable intermediates along the hydrogenolysis pathway suggests that the closure is rapid, even at such a congested center. However, unlike the acylating closures, it is conceivable that the alkylation takes place prior to the reductive amination.[42]

**Synthesis of 7-Epiaustraline.** Completion of the synthesis of 7-epiaustraline required three operations; the removal of the silyl ether protecting group, the hydrolysis of the benzoate, and the Si to O conversion. All three steps were conveniently accomplished with the Tamao−Fleming oxidation,[43] Scheme 8. Amine **34** was first protected by protonation with methanesulfonic acid and then treated with mercury (II) acetate and a 32% solution of peroxyacetic acid in acetic acid and heated for 14 h at 40 °C.[44] After purification by ion exchange chromatography, the *N*-oxide was reduced by hydrogenolysis over 10% Pd−C in methanol/acetic acid. Final purification by ion exchange chromatography provided

(39) Denmark, S. E. *J. Org. Chem*. **1981**, *46*, 3144.
(40) (a) Ramaswamy, S.; Prasaid, K.; Repic, O. *J. Org. Chem*. **1992**, *57*, 6344. (b) Review of cyclic sulfate chemistry: Lohray, B. B. *Synthesis* **1992**, 1035.
(41) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett*. **1989**, *30*, 655.
(42) For an in depth discussion of he consequences of staging the hydrogenolysis, see ref 17a.
(43) Fleming, I. *Chemtracts: Org. Chem*. **1996**, *9*, 1.
(44) Rehders, F.; Hoppe, D. *Synthesis* **1992**, 865.

a solid in 19−25% yield. Substitution of mercury(II) trifluoroacetate resulted in a dramatic increase in yield. Amine **34** was allowed to react with $Hg(O_2CCF_3)_2$ in a mixture of trifluoroacetic acid and acetic acid for 1 h to effect protiodephenylation.[45,46] The reaction mixture was diluted with acetic/peroxyacetic acid at 0 °C and then was heated at 50 °C for 24 h. The *N*-oxide was isolated by ion exchange chromatography and subsequently reduced ($H_2$, 10% Pd−C, MeOH/HOAc). Final purification on analytical grade Dowex (H-form) provided 7-epiaustraline (**4**) in 74% yield. Recrystallization from MeOH−$CHCl_3$ provided an analytically pure sample in 61% yield.[47] The tetrol was peracetylated and the enantiomeric excess determined by CSP supercritical fluid chromatography to be 97% ee.[48]

**Scheme 8**




**34** 61% (−)-7-epiaustraline (−)-(**4**)

**Structural Verification and Assignment.** The $^1$H NMR spectrum of the final product did not match the data reported in the literature.[7] Moreover, the $^1$H NMR spectrum of synthetic (−)-**4** did not match the data reported for any of the known alexine isomers. In addition, the product from our synthesis was a levorotatory solid (mp 161 °C) whereas the substance reported as 7-epiaustraline is described as a dextrorotatory oil.[7] Repeated purification of a sample of (−)-**4** afforded crystals suitable for X-ray analysis. The crystal structure (see the Supporting Information) left no doubt that the synthetic plan was successfully executed and indeed delivered 7-epiaustraline. Thus, although the synthesis of the target structure was complete, we had unambiguously established that (1*R*,2*R*,3*R*,7*R*,7a*R*)-hexahydro-3-(hydroxymethyl)-1*H*-pyrrolizine-1,2,7-triol ((−)-**4**) was not the material isolated by Nash et al.[49] While outside our purview, we were nonetheless mystified as to the nature of the material reported in the literature as 7-epiaustraline.[22]

Comparison of the $^1$H NMR data for the isolated material with data obtained for our compound and for the sample of 7-epiaustraline (**4**) provided by Pearson[12,50] revealed several interesting differences, Table 4. Examination of the coupling constants between *H*C(1), *H*C(2), and *H*C(3) was particularly informative. The coupling constants for those protons from the Pearson sample were similar to those of the compound prepared by our synthetic route. Values of $J = 8-9$ Hz were consistent with an all-*trans* relationship between those protons.

An all-*trans* relationship in the fully substituted five-membered ring can be satisfied by four of the known australine/alexine isomers: alexine (**1**), 7-epialexine (**9**), australine (**2**), and 7-epiaustraline (**4**). The coupling between *H*C(1) and *H*C(7a) for material prepared by Pearson and ourselves was 7.6−7.8 Hz, suggesting a *trans*-relationship between those protons. A *trans*-relationship between *H*C(1) and *H*C(7a) precludes the alexines as possible isomers. That leaves australine and 7-epiaustraline as potential candidates for the identity of the material synthesized by Pearson[12] and isolated by Nash et al.[7] The remaining coupling constant, *H*C(7a)−*H*C(7), was determined to be 2 Hz in the synthetic material prepared herein. A value of 4.4 Hz was found in the data supplied by Pearson.[50] In australine, the value of the same proton coupling was reported as 5 Hz.[7] Comparison of all three values points to a closer match between Pearson's sample and australine. In fact, australine was the synthetic target identified by Pearson. When compared to the Nash data, those for Pearson's synthetic material matched that of isolated 7-epiaustraline. They were forced to invoke a curious inversion of an epoxide stereogenic center during the crucial epoxide opening reaction to explain the synthesis of 7-epiaustraline instead of australine. A subsequent reevaluation of the published data for australine indeed confirm that the material originally assigned the structure of 7-epiaustraline is indeed australine itself.[22] Thus, Pearson et al. did in fact succeed in synthesizing their intended target, but chose not to challenge the assignment when the data did not match. In sum, 7-epiaustraline is not (yet) a naturally occurring pyrrolizidine.

**Synthesis of 1-Epicastanospermine.** The synthetic strategy detailed in Scheme 1 requires a selective activation of the primary alcohol of diol **30** to provide the requisite precursor for 1-epicastanospermine. Treatment of the diol **30** with 4-toluenesulfonyl chloride resulted in the slow consumption of the starting material and the formation of the primary tosylate **35**, Scheme 9. Substitution of 2,6-lutidine for pyridine improved the yield of **35** to 95%. Replacing 4-toluenesulfonyl chloride with the anhydride decreased the reaction times and simplified purification. The tosylate was unstable in its pure form and had to be hydrogenolyzed in the presence of residual 2,6-lutidine. We were able to secure the unstable epoxide **36** from **35** through the action of potassium *tert*-butoxide.

Although the cyclic sulfate **31** had provided the indolizidine selectively (4/1), we hoped to find a precursor that exclusively produced this ring system. Thus, the epoxy nitroso acetal **36** was first examined. Hydrogenolysis of **36** provided a low yield of pyrrolizidine **33** whose $^1$H NMR spectrum was identical to the material from the hydrogenolysis of the cyclic sulfate **31** and mesylate **29**,

(45) Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *Perkin Trans. 1* **1992**, 2735.

(46) A $^1$H NMR study indicated that the dephenylation required <20 min.

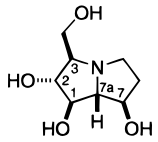
(47) The procedure was found to be reproducible within the 0.06−0.25 mmol range resulting in the isolation of 7-epiaustraline in 68−77% yield. Application of the exact conditions on a 1 mmol scale gave a much lower yield (31%). The *N*-oxide eluted over a considerable length of time during the ion exchange purification suggesting that binding the presence of mercury salts was a source of the problem. Reducing the quantity of $Hg(O_2CCF_3)_2$ from 7.5 equiv to 1.5 equiv. did not affect the yield of the process but did slightly improve the elution of the *N*-oxide.

(48) Analytical CSP supercritical fluid chromatography was performed by Robert Stavenger.

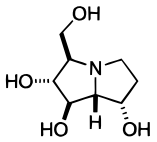
(49) GC-MS analysis of the persilylated product (−)-**4** clearly showed that it was different from the natural material and also different from (+)-australine. This ruled out the possibility that the spectroscopic discrepancies resulted from the formation of salts (carbonates, hydrates, or silicates) in the isolation of the natural product. We are grateful to Dr. R. J. Nash (Aberystwyth) for graciously performing those analyses.

(50) We are grateful to Professor William Pearson (University of Michigan) for kindly supplying spectral data for his synthetic 7-epiaustraline.

**Table 4. $^1$H and $^{13}$C Data for 7-Epiaustraline (4) and Australine (2)**




7-epiaustraline

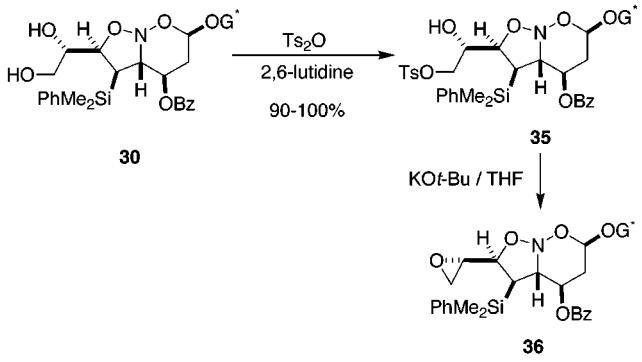



australine

| nucleus | isolated[a] | Pearson[b] | this work[c] | this work[d] | australine[e] |
|---|---|---|---|---|---|
| *H*C(1) | 4.02 (dd) | 4.06 (t, $J$ = 7.7) | 3.54 (t, $J$ = 8.1) | 3.58 (t, $J$ = 7.8) | 4.41 (dd, $J$ = 5) |
| *H*C(2) | 3.70 (dd) | 3.73 (t, $J$ = 8.8) | 3.58 (t, $J$ = 8.5) | 3.71 (dd, $J$ = 8.5, 7.8) | 3.92 (dd, $J$ = 9, 5) |
| *H*C(3) | 2.50 (m) | 2.58 (m) | 2.50 (ddd, $J$ = 9.3, 6.3, 3.9) | 2.68 (ddd, $J$ = 9.0, 6.1, 3.4) | 3.03 (m) |
| *H*C(5) | 2.97 (m) | 3.00 (m) | 2.90 (ddd, $J$ = 11.5, 10.3, 5.9) | 3.24 (m) | 3.18 (m) |
| | 2.50 (m) | 2.58 (m) | 2.70 (ddd, $J$ = 11.0, 7.1, 3.4) | 2.98 (ddd, $J$ = 11.2, 7.1, 2.7) | 2.93 (m) |
| *H*C(6) | 1.85 (m) | 1.85 (m) | 1.90 (m) | 2.77 (ddt, $J_d$ = 13.2, 5.4; $J_t$ = 2.7) | 2.02 (m) |
| | 1.73 (m) | 1.79 (m) | 1.60 (ddt, $J_d$ = 12.7, 6.1; $J_t$ = 3.4) | 2.02 (m) | |
| *H*C(7) | 4.19 (m) | 4.21 (m) | 4.18 (dt, $J_d$ = 4.6; $J_t$ = 2.7) | 4.28 (dt, $J_d$ = 4.4; $J_t$ = 2.2) | 4.58 (dd, $J$ = 9, 5) |
| *H*C(7a) | 2.98 (dd) | 3.05 (dd, $J$ = 7.6, 4.4) | 2.84 (dd, $J$ = 7.8, 2.0) | 3.16 (dd, $J$ = 7.8, 1.5) | 3.46 (dd, $J$ = 5) |
| *H*C(8) | 3.59 (dd) | 3.63 (dd, $J$ = 11.8, 3.4) | 3.60 (dd, $J$ = 11.7, 3.9) | 3.75 (dd, $J$ = 11.2, 3.4) | 3.81 (dd, $J$ = 12, 4) |
| | 3.42 (dd) | 3.45 (dd, $J$ = 11.9, 6.6) | 3.46 (dd, $J$ = 11.7, 6.3) | 3.60 (dd, $J$ = 11.5, 6.1) | 3.64 (dd, $J$ = 12, 6.5) |
| C(1) | 73.8 | 73.9 | 77.5 | 79.8 | 74.9 |
| C(2) | 71.4 | 71.7 | 75.9 | 77.4 | 77.3 |
| C(3) | 71.2 | 71.4 | 67.9 | 71.3 | 72.9 |
| C(5) | 52.5 | 52.7 | 51.4 | 53.5 | 54.9 |
| C(6) | 35.8 | 35.9 | 33.1 | 33.1 | 38.1 |
| C(7) | 79.7 | 79.5 | 74.8 | 77.2 | 75.8 |
| C(7a) | 70.2 | 70.3 | 73.5 | 76.1 | 68.9 |
| C(8) | 63.5 | 63.1 | 62.3 | 63.1 | 65.6 |

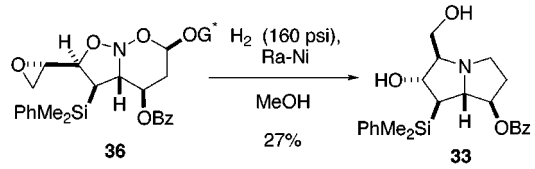
[a] Spectra taken in $D_2O$ and assigned by COSY.[7] These data have subsequently been shown to be those for austraine.[22] [b] Spectra taken in $D_2O$ and assigned by comparison with data for isolated material.[12] [c] Spectra taken in $D_2O$ and assigned by COSY.[4] [d] Spectra taken in $CD_3OD$ and assigned by COSY. [e] Spectra taken in $D_2O$ and assigned by COSY. These data have subsequently been shown to be those for 1-epiaustraline.[22]

**Scheme 9**




Scheme 10. The major product was unidentifiable, but most certainly not **32**.

**Scheme 10**



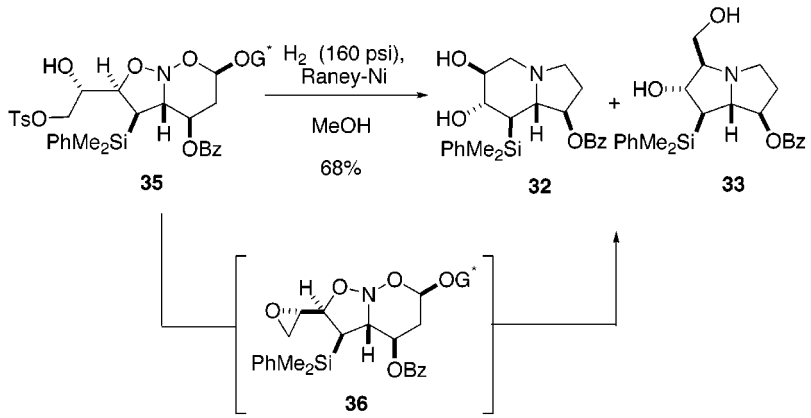

We next turned to primary tosylate **35** which should be capable of producing only the indolizidine skeleton. Surprisingly, hydrogenation of **35** at 260 psi over Raney nickel afforded a 1/4 mixture of indolizidine **32** and pyrrolizidine **33**, Scheme 11. The formation of **33** suggested the intervention of a competing pathway involving a base-mediated epoxide formation followed by 5-*exo-tet* ring opening.[51] The amount of **33** could be minimized by washing the Raney nickel thoroughly with $H_2O$. To maximize reproducibility, several washings with pH 7 buffer were included. With these precautions, a 14/1 ratio ($^1$H NMR) of **32** to **33** could be obtained. The hydrogenolysis of tosylate **35** exhibited a modest pressure effect. For example, at 160 psi of $H_2$, the amines **32** and **33** were isolated in a 8/1 ratio in 79% yield. At 260 and 360 psi, a 12/1 ratio of the amines was observed, albeit in variable yields (75% at 260 psi and 66% at 360 psi). Under the final optimized procedure, diol **30** was transformed into a mixture of amines **32** and **33** (8/1 by $^1$H NMR analysis) in addition to recovered auxiliary (94%). The amines were separated and isolated in 64% and 4% yields, respectively. Analysis of the $^3J_{H,H}$ coupling constants of the indolizidine **32** was consistent with an all *trans*-relationship in the six-membered ring.

The divergence of selectivity in the opening of the cyclic sulfate **31** and epoxide **36** merits comment. In both cases the formation of the pyrrolizidine nucleus involves a 5-*exo-tet* closure. However, the indolizidine formation requires a 9-*endo-tet* closure from **31** as compared to a 7-*endo-tet* closure from **36**.[52] According to Baldwin,[51] 5-*exo-tet* is preferred over 6-*endo-tet* pathway, but the preference over higher order endocyclic closures is not established. Since the basis of the Eschenmoser/Baldwin postulate is the overlap of the approaching nucleophile with the $\sigma^*$ orbital of the carbon bearing the leaving group, the two components should ideally achieve an alignment approximating 180°. In the cyclic sulfate, the trajectory of displacement at the terminus (9-*endo-tet*) is nearer to that angle than at the internal carbon (the

(51) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939.

(52) Rigorously, to compare endocyclic and exocyclic $S_N2$ reactions the nucleofuge must be counted as part of the endocyclic process. Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059.

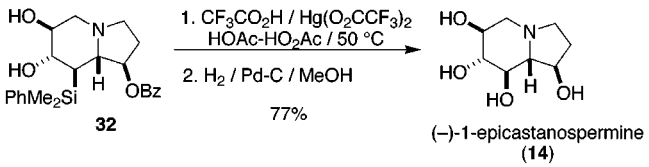
**Scheme 11**




accessibility of a primary versus a secondary center notwithstanding). In contrast, the reverse is true for the epoxide. The net effect in the nucleophilic opening of cyclic electrophiles is that the size of the ring containing the nucleofuge dramatically affects the orientation of the interacting orbitals and thus alters the selectivity.

Completion of the synthesis of 1-epicastanospermine required the same three operations as were mandated in the synthesis of 7-epiaustraline. Again, all three steps were conveniently accomplished with the Tamao−Fleming oxidation, Scheme 12. Thus, amine **32** was allowed to react with $Hg(O_2CCF_3)_2$ in trifluoroacetic acid for 1 h to effect dephenylation of the silane.[44] The reaction mixture was diluted with acetic/peroxyacetic acid and was heated at 50 °C for 14 h. The *N*-oxide was isolated by ion exchange chromatography and subsequently reduced ($H_2$, 10% Pd−C, MeOH−HOAc). Final purification on analytical grade Dowex (H form) followed by chromatography on Reverse Phase silica gel (C-18) ($CHCl_3$/MeOH/$NH_4OH$, 1/0/0, 90/9/1 then 20/5/1) provided 1-epicastanospermine (**14**) as an oil in 77% yield. An analytical sample of the amine was obtained by conversion to its HCl salt. Recrystallization of the salt from MeOH−$Et_2O$ and MeOH−$CHCl_3$ afforded an analytically pure hydrochloride, **14**·HCl. The free base was then obtained from the analytical sample by ion exchange chromatography (Dowex OH-form) for the purposes of comparison with reported data. The $^1H$ NMR spectrum of the synthetic material was identical to that reported in the literature.[19]

**Scheme 12**




**Optical Rotation.** While the spectroscopic data matched, the optical rotation data for synthetic **14** was clearly at variance with the literature values. The optical rotations and individual starting materials for the reported syntheses of 1-epicastanospermine are compiled in Table 5. With the exception of Mulzer[53b] (who synthesized *ent*-**14**), all the authors claimed the successful preparation of the targeted (1*R*,6*S*,7*R*,8*R*,8a*R*)-octahydro-1,6,7,8-indolizinetetrol (**14**) in addition to (1*S*,6*S*,7*R*,8*R*,8a*R*)-octahydro-1,6,7,8-indolizinetetrol [(+)-castanospermine (**13**)]. The huge variation in magnitude

**Table 5. Rotation Data for 1-Epicastanospermine (14)**

| starting material | **14** $[\alpha]_D$ | reference |
|---|---|---|
| D-mannose | −39.1° ($c$ = 0.4, $H_2O$) | Hashimoto[53a] |
| D-xylose | −4° ($c$ = 0.3, MeOH) [*ent*-**14**] | Mulzer[53b] |
| D-glucose | +6° ($c$ = 0.45, $H_2O$) | Ganem[53c] |
| D-glucofuranurono-6,3-lactone | (−) | Anzeveno[53d] |
| dimethyl L-tartrate | +3.8° ($c$ = 0.5, MeOH) | Kibayashi[19] |
| D-glucofuranurono-6,3-lactone | −5° ($c$ = 0.1, $H_2O$) | Stütz[53e] |

and sign of the rotation is immediately apparent. Mulzer has effectively demonstrated the dependence of optical rotation on pH by measuring the rotation of *ent*-**14** at pH 7.1, 6, and 5. At those pH levels, $[\alpha]_D^{20}$ values of −21, −10, and +4 were obtained. In addition, the authors determined the rotation in MeOH ($[\alpha]_D^{20}$ −4), presumably to minimize pH effects. Kibayashi also measured the rotation of 1-epicastanospermine in MeOH and found the value to be +3.8.[19]

Due to the small magnitude of α, it is likely that trace quantities of impurities or salts will affect both the sign and magnitude of the rotation.[54] Our sample of **14** had the following rotation values: $[\alpha]_D^{23}$ +18.25° ($c$ = 1.23, $H_2O$) for the HCl salt, $[\alpha]_D^{23}$ −5.31° ($c$ = 0.83, $H_2O$, pH 9.7) and $[\alpha]_D^{23}$ −3.10° ($c$ = 1.86, MeOH) for the free base. The absolute configuration of our compound was secured from the single-crystal X-ray analysis of nitroso acetal (−)-**27a** which leads to (1*R*,6*S*,7*R*,8*R*,8a*R*)-**14**. The purity of (−)-1-epicastanospermine was assured through conversion to the HCl salt. The free amine was obtained from the analytically pure salt by passage through a Dowex column (OH-form) eluting with distilled $H_2O$.[55] The pH of the aqueous solution of **14** used to measure the rotation was determined to be 9.7, a clear indication that the amine was in the free base form. As a result there is no

(53) (a) Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617. (b) Mulzer, J.; Dehmlow, H.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1992**, *57*, 3194. (c) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165. (d) Anzeveno, P. B.; Angell, P. T.; Creemer, L. J.; Whalon, M. R. *Tetrahedron Lett.* **1990**, *31*, 4321. (e) Graβberger, V.; Berger, A.; Dax, K.; Fechter, M.; Gradnig, G.; Stütz, A. E. *Liebigs Ann. Chem.* **1993**, 379.

(54) For discussion of the use of polarimetry, see (a) Lyle, G. G.; Lyle, R. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 1; Chapter 2. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Carbon Compounds*; Wiley: New York, 1994; pp 1071−1080.

(55) The discrepancy with the rotation of 6-epicastanospermine was solved in a similar manner. The rotation was measured on a sample of the analytically pure HCl salt in 0.1 M NaOH in MeOH: Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700.

question that the rotation value of **14** under the conditions indicated is $[\alpha]_D^{23}$ −5.31° ($c$ = 0.83, $H_2O$, pH 9.7).

## Conclusions

The successful preparation of (−)-7-epiaustraline (9 steps, 23% yield, 97% ee) and 1-epicastanospermine (10 steps, 20% yield, and 97% ee) was accomplished by extending the tandem [4 + 2]/[3 + 2] cycloaddition strategy to include an alkylation in the hydrogenolysis step. The strategy was divergent and allowed for the preparation of two classes of natural products from a common intermediate. Central to the strategy was the highly regio- and stereoselective [3 + 2] cycloaddition of nitronate (+)-**15** with alkoxymethyl (*Z*)-*β*-silylvinyl ketones and the highly selective reduction of the resulting ketone **24a** with L-Selectride. The structure of (−)-7-epiaustraline was secured by single crystal X-ray analysis which served to initiate a reevaluation of the structures of naturally isolated australines. The optical rotation of (1*R*,6*S*,7*R*,8*R*,8a*R*)-**14** has been reevaluated to be levorotatory on the basis of this work.

**Acknowledgment.** We are grateful to the National Institutes of Health (GM-30938) for generous financial support. We also acknowledge Drs. G. W. J. Fleet, M. A. Wormald (Oxford), R. J. Nash (Aberystwyth), and Prof. W. H. Pearson (Michigan) for helpful exchange of information.

**Supporting Information Available:** The general experimental methods and full experimental, spectroscopic, and analytical details ($^1$H NMR, $^{13}$C NMR, IR, MS, TLC, $[\alpha]_D$) for all new compounds along with $^1$H and $^{13}$C NMR spectra for (−)-7-epiaustraline and (−)-1-epicastanospermine; crystallographic parameters, atomic coordinates, bond lengths and angles for (−)-**4**, (−)-**26a**, (−)-**27a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991990D